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A Tale of Timing and Transport

Excitatory and inhibitory synapses show long-term plasticity, but spike timing-dependent plasticity was seen only at excitatory connections. No longer. In this issue of *Neuron*, Woodin et al. demonstrate that coincident pre- and postsynaptic activity acts on the neuronal K^+/Cl^- cotransporter KCC2 to shift the reversal potential for Cl^- and thus alters the effectiveness of GABAergic synapses.

When it comes to personalized car license plates, California tops the list. Judged by vanity plates like "LTP," "LTD," "AMPA," "GABA," or "SYNAPSE," California also is the homeland of neuroscientists flaunting plasticity. One car proudly promotes "KCC2," which is fully understandable given the functions of this K^+/Cl^- cotransporter. It is responsible for extruding both K^+ and Cl^- from neurons, thus effectively regulating intraneuronal Cl^- concentration or buffering extracellular K^+ (Payne et al., 2003). During developmental plasticity, by the time neurons reach their maturity, upregulation of KCC2 activity switches depolarizing GABA responses into hyperpolarizing ones (Rivera et al., 1999; Ganguly et al., 2001). The new study by Woodin et al. (2003), in this issue of *Neuron*, demonstrates a role of KCC2 in neuronal plasticity beyond that already known to take place during development. Actually, almost the reverse of the developmental regulation of intracellular Cl^- concentration seems to occur during spike timing-dependent plasticity at GABA synapses. This remarkable plasticity can be elicited in cultured neurons and hippocampal slices when inhibitory terminals are stimulated at 5 Hz for 30 s and the postsynaptic cell is induced to fire action potentials within 20 ms of the presynaptic stimulation. In contrast to excitatory synapses, where a postsynaptic spike that precedes the EPSP promptly punishes the ineffective synapse by inducing LTD (Markram et al., 1997; Abbott and Nelson, 2000), the GABA reversal potential becomes altered, regardless of whether the action potential precedes or succeeds the presynaptic stimulation within this time limit (Woodin et al., 2003). But Ca^{2+}, as always, is involved. The postsynaptic neuron's action potential triggers Ca^{2+} entry through nifedipine-sensitive voltage-gated Ca^{2+} channels, and this Ca^{2+}, through a yet unknown pathway, reduces the function of KCC2. Thus, less Cl^- will be extruded from the cell, and accordingly, the GABA reversal potential (E_{GABA}) will become more depolarizing. This may even convert a normally inhibitory synapse into an excitatory one through passively propagated depolarization (Stein and Nicoll, 2003). A depolarization-dependent lasting shift in E_{GABA}, termed long-term transformation (LTT), has been previously described in molluscan and hippocampal neurons (Collin et al., 1995), but its Ca^{2+} dependence and the involvement of KCC2 have not been revealed.

The most remarkable feature of the transporter-dependent GABA synapse plasticity is its synapse specificity. In paired and triplet recordings, Woodin et al. (2003) demonstrate that this novel type of plasticity mostly affects dendritic GABA synapses, as expected from the predominantly dendritic distribution of KCC2 (Gulyás et al., 2001), and most interestingly, it may be restricted to the stimulated synapse (Figure 1). How does such a highly localized alteration in $[Cl^-]_i$ take place inside a neuron's dendrite? Does the KCC2 transporter in the vicinity of the stimulated synapse become tagged somehow? Although there is no experimental evidence presented in the study, one possibility is that KCC2 molecules located near a GABA synapse stimulated 150 times at 5 Hz become altered. This alteration renders them sensitized to second messenger effects of Ca^{2+}. At the holding potentials used in the experiments, the GABA receptors at the synapses studied by Woodin et al. (2003) released Cl^- into the extracellular space. This may have led to a local depletion of $[Cl^-]_i$ which together with an extracellular K^+ accumulation resulting from the presynaptic repetitive stimulation could have reversed the direction of ion transport by KCC2 (Payne, 1997; DeFazio et al., 2000). It remains to be determined if the activity of KCC2 can be more readily altered by Ca^{2+} or related second messengers when it functions in reverse, i.e., pumps Cl^- and K^+ into the cell. If this scenario proves to be correct, the spike timing-dependent plasticity would be limited only to synapses in which E_{GABA} is more positive than the neuron's resting membrane potential.

Now that both glutamate and GABA synapses show spike timing-dependent plasticity, it will be challenging to sort out how the coincidence of postsynaptic spiking and presynaptic activity regulate the two types of synaptic activity in concert (Abbott and Nelson, 2000). Clearly, the firing of action potentials will be mostly initiated by excitatory synapses. If a cell fires within 20 ms *after* a presynaptic action potential is triggered at excitatory or inhibitory terminals, both types of connections will be strengthened. In contrast, if the postsynaptic cell discharges $<$20 ms *before* a presynaptic spike in both types of terminals, a synaptic imbalance may result between the depression of the excitatory synapse seen in most cells and the reinforcement of the inhibitory connection. The functional significance of this complex interplay of synaptic plasticity will initiate more exciting research, perhaps involving new molecules worthy to be engraved on more Californian license plates. As of August 1, 2003, "NMDA" was still available. Any takers?

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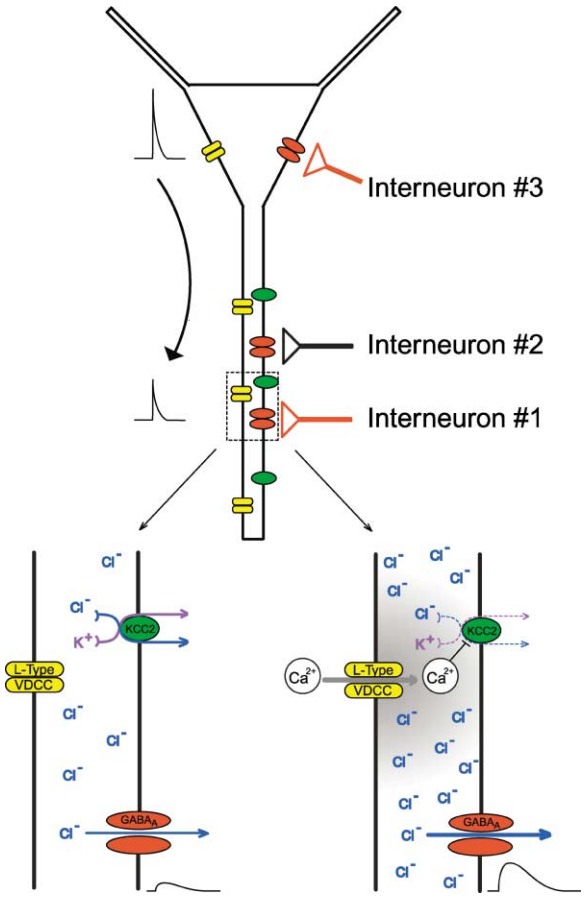

Figure 1. Schematic Representation of Spike Timing-Dependent Plasticity of a GABA Synapse in a CA1 Pyramidal Cell

A train of back propagating action potentials (triggered at a frequency of 5 Hz by somatic current injections) invades the apical dendrites of a pyramidal cell, thus activating nifedipine-sensitive (L-type) voltage-dependent Ca^{2+} channels (VDCC). When a GABAergic synapse (e.g., that formed by interneuron #1 in the figure) is stimulated such that individual synaptic events occur within 20 ms of the postsynaptic action potentials, the resulting influx of Ca^{2+} (dark cloud on lower right panel) suppresses the activity of neighboring K^+/Cl^- cotransporters (KCC2). As the recordings were made at a membrane potential hyperpolarized from the Cl^- reversal potential (E_{Cl}), the diminished KCC2 mediated Cl^- extrusion leads to a local intracellular accumulation of Cl^- resulting in larger GABAergic postsynaptic potentials. Remarkably, this spike timing-dependent plasticity of the E_{Cl}, and hence of GABAergic transmission, is synapse specific. Only the function of the synapse formed by interneuron #1 in the figure is altered because it is the only one that fulfills the following two requirements. (1) It is active (indicated by red in the figure) within 20 ms of each postsynaptic action potential and (2) is located on a KCC2-rich apical dendrite of a pyramidal cell. Another dendritic GABA synapse, that formed by interneuron #2, does not display the plasticity, because it was not active during the firing of the action potentials. Because of the paucity of KCC2 on pyramidal cell somata (Gulyás et al., 2001), the somatic synapse formed by interneuron #3 will not display spike timing-dependent plasticity, even if it were active during the train of action potentials.

Selected Reading

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Making Space for Rats: From Synapse to Place Code

The formation of spatial memories is believed to depend on long-term potentiation (LTP) of synapses within the hippocampal network. In this issue of *Neuron*, Dragoi et al. demonstrate that LTP can cause changes in the hippocampal representation of space without disrupting network dynamics. These results help define the elusive relationship between cellular-level synaptic plasticity and systems-level neural coding.

For 30 years, hippocampal researchers have known that high-frequency stimulation of hippocampal projections produces immediate and long-lasting changes in synaptic strength. This hours-long increase in potentiation of synaptic weights is known as long-term potentiation (LTP) (Bliss and Lomo, 1973). For about 30 years, we have also known that the principal cells of the rat hippocampus have the nifty property of firing robustly when the rat is in a particular location and being essentially silent when the rat is walking around outside of that place (O'Keefe and Dostrovsky, 1971). The development of these "place fields" happens within minutes of exposure to a new location (Wilson and McNaughton, 1993).

It seems likely that the changes in synaptic strength associated with LTP underlie the rapid formation of place fields, but a direct link has not been established. We know that LTP is particularly easy to induce at hippocampal synapses and that pharmacological or genetic disruption of LTP causes spatial learning impairments (Morris et al., 1986; Nakazawa et al., 2003). Thus, while it is clear that LTP plays an essential role in spatial processing in rodents, the precise nature of that role is not known. In order to link mechanisms of synaptic strengthening and mechanisms of spatial learning, Dragoi et al. (2003 [this issue of *Neuron*] investigated the effects of LTP on the place-related firing of hippocampal cells.

Dragoi et al. induced LTP in awake, freely behaving